Neuroprotective Effect of Mild Hypothermia in Patients Undergoing Coronary Artery Surgery With Cardiopulmonary Bypass

A Randomized Trial

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Background—Neuropsychological deficits occur in 30% to 80% of patients undergoing heart surgery and are due in part to ischemic cerebral injury during cardiopulmonary bypass. We tested whether mild hypothermia, the most efficacious neuroprotective strategy found in laboratory studies, improved cognitive outcome in patients undergoing coronary artery surgery.

Methods and Results—Patients 60 years or older scheduled for coronary artery surgery were enrolled. During cardiopulmonary bypass, patients were initially cooled to 32°C then randomly assigned to rewarming to 37°C (control) or 34°C (hypothermic), with no further intraoperative warming. Testing was scheduled preoperatively and 1 week and 3 months postoperatively. Eleven tests were combined into 3 cognitive domains: memory, attention, and psychomotor speed and dexterity. A patient was classified as having a cognitive deficit if a decrease of ≥0.50 SD was realized in 1 or more domains. The incidence of cognitive deficits 1 week after surgery, which was the primary outcome, was 62% (62/100) in the control group and 48% (45/94) in the hypothermic group (relative risk 0.77, $P=0.048$). In the hypothermic group, the magnitude of deterioration in attention and in speed and dexterity was reduced by 55.6% ($P=0.038$) and 41.3% ($P=0.042$), respectively. At 3 months, the hypothermic group still performed better on one test of speed and dexterity (grooved pegboard). There was no difference in morbidity or mortality.

Conclusions—Our findings support a neuroprotective effect of mild hypothermia in patients undergoing coronary artery surgery and should encourage physicians and perfusionists to pay careful attention to brain temperature during cardiopulmonary bypass. **(*Circulation*. 2001;104[suppl I]:I-85-I-91.)**

Key Words: cerebral ischemia ■ cardiopulmonary bypass ■ trials ■ brain ■ nervous system

More than 600 000 patients undergo coronary artery surgery with cardiopulmonary bypass (CPB) in North America each year. Thirty percent to 80% of these patients suffer a decline in cognitive functioning as demonstrated by neuropsychometric testing during the first postoperative month.[1] This incidence is higher than in patients of similar age undergoing major surgery not requiring CPB.[2] It is likely that ischemic brain injury occurring during the cardiac procedure is the cause of the excess incidence of deficits.[3,4] Lowering brain temperature by 2°C to 5°C during ischemia (mild intraischemic hypothermia) is the most efficacious neuroprotective strategy to have been found in laboratory studies.[5] However, the efficacy of this promising neuroprotective strategy has been difficult to demonstrate in humans. Patients undergoing coronary artery surgery present a unique opportunity to test the effects of mild hypothermia in a setting in which ischemic cerebral injury is frequent and temperature is easily controlled. We sought evidence of a neuroprotective effect of mild hypothermia by conducting a randomized trial wherein patients undergoing coronary artery surgery with CPB were assigned to an extended period of hypothermia (34°C) or normothermia (37°C). The primary outcome was the incidence of cognitive deficits in the early postoperative period.

Methods

Patients

Between August 1995 and February 1998, patients older than 60 years who had been accepted for CABG at the University of Ottawa Heart Institute were asked to give informed consent for enrollment in this trial, which was approved by our Institutional Review Board. The procedures followed were in accordance with institutional guidelines. Patients (n=294) without a history of neurological deficits who were fluent in English and had no impediment to completing neuropsychological testing were asked to come for preoperative testing within 3 months of surgery (Figure 1); 234 consented. An extended mental state examination (Modified Mini-Mental State [3 MS] examination, inclusion score >77) and the

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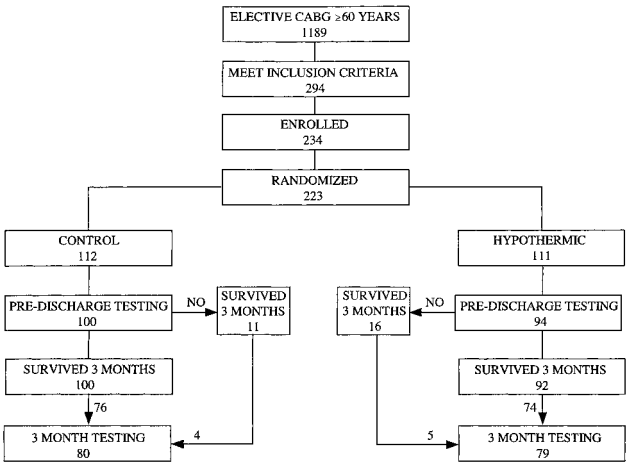

Figure 1. Patient flow diagram. Of 234 patients who completed preoperative testing, 11 were excluded before randomization: 2 in whom history of stroke or head injury was discovered, 2 who declined immediately before surgery, 1 who withdrew at surgeon's request, 3 in whom CPB was not used, 2 who had femoral instead of aortic cannulation, and 1 for whom the randomization envelope was never opened. Of 223 patients randomized, 29 were not tested early postoperatively (21 refused, and 8 were too sick). Of these 29, 9 returned for 3-month visit.

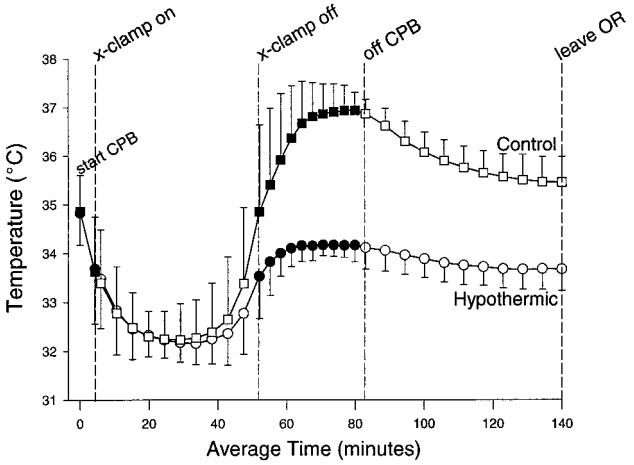

Figure 2. Intraoperative nasopharyngeal temperature (mean±SD). Because duration of procedure was different for each patient, a common time base was constructed. This was done by division of intraoperative period into 3 intervals (cross-clamp on to cross-clamp off, clamp off to off CPB, and off CPB to leave operating room [OR]) and, for each patient, subdivision of each interval into 10 equal subintervals. In this way, all patients had 10 temperature values for each interval that were averaged within each group. Actual duration in minutes of a subinterval would vary with interval time of a particular patient. For illustrative purposes, average duration of each interval for entire study group was used to label abscissa. x-clamp indicates aortic cross-clamp.

Canadian Neurological Scale[6] were used to screen patients for cognitive or neurological impairment. No one was excluded on either basis. Eleven patients were excluded after the preoperative visit but before randomization, leaving 223 who were randomly assigned, 112 to the control group and 111 to hypothermia. Only 1 patient did not receive the assigned treatment. That patient was assigned to hypothermia but was rewarmed to 37°C after requiring CPB a second time.

Intraoperative Protocol and Randomization

After induction of anesthesia, a temperature probe was placed in the nasopharynx, and this temperature was monitored and controlled throughout the intraoperative period. Our earlier studies had shown that nasopharyngeal temperature is the most reliable indicator of brain temperature in this setting. Bladder temperature was used as an indicator of visceral temperature. Tranexamic acid was given to patients who had previous CABG, to reduce blood loss. CPB was performed with membrane oxygenators and arterial line filters (43 μm, Cobe) with nonpulsatile flow at 2.5 to 2.8 L/min per square meter of body surface area. Mean arterial pressure was maintained between 50 and 80 mm Hg with phenylephrine or isoflurane as needed. During hypothermia, an alpha-stat strategy was used (blood gases were not temperature corrected). On initiation of CPB, patients were immediately cooled to 32°C. After application of the aortic cross-clamp, cardiac arrest was induced and maintained with antegrade cold crystalloid cardioplegia. When the surgeon asked for rewarming to begin, usually 10 minutes before release of the aortic cross-clamp, the perfusionist opened an opaque envelope that concealed the treatment assignment, which had been determined by computer-generated random numbers in blocks of 8, with prestratification for age 60 to 74 and older than 75 years. Over the next 10 minutes, blood in the oxygenator was warmed so that nasopharyngeal temperature increased to either 34°C or 37°C. These temperatures were kept constant until separation from CPB (Figure 2). In the recovery room, warming blankets were applied.

Neuropsychometric Testing

Learning efficiency and memory consolidation were evaluated with a verbal list-learning procedure (Buschke Selective Reminding administration and scoring). Alternate forms were used to reduce practice effects. Attention span was evaluated with the Wechsler Adult Intelligence Scale-Revised (WAIS-R) Digit Span. Psychomotor speed and dexterity were measured by Trails A and B, grooved pegboard, and the Symbol Digit Modalities Test (oral administration). From these tests, we calculated the following measures: (1) Buschke total learning free recall; (2) Buschke consistent long-term retrieval; (3) Buschke long-term retrieval; (4) Buschke long-term storage; (5) Buschke delayed recall; (6) Digit Span Forward; (7) Digit Span Backward; (8) Trails A; (9) Trails B (maximum score 300 seconds); (10) grooved pegboard (dominant hand, maximum score 300 seconds); and (11) Symbol Digit Modalities Test. Preoperative and postoperative measures of mood (Geriatric Depression Scale) and anxiety (State-Trait Anxiety Inventory) were obtained for use as covariates. Early and late postoperative testing was planned for 7 days and 3 months after surgery, respectively. The psychometrist and the patient were unaware of the treatment assignment.

The Canadian Neurological Scale[6] was used to detect neurological deficits. Patients were tested preoperatively and early and late postoperatively, as well as on the first postoperative day, to detect intraoperative events. Assessors, who were trained with materials provided by the developers, were unaware of the treatment assignment.

Safety Outcomes

Bleeding from the chest and mediastinal tubes during the first 12 postoperative hours was recorded. ECGs taken 2 hours, 1 day, and 2 to 5 days postoperatively were assessed. Myocardial infarction was defined as the appearance of new Q waves >0.04 seconds in duration. Creatine kinase (CK) was measured 2 hours postoperatively and on the morning after surgery. CK-MB fraction was determined if total CK was >1000 U/L. Chest and leg wound infections were diagnosed by established criteria.[7]

Statistical Analysis

The 11 neuropsychometric tests were grouped into 3 cognitive domains: memory, speed, and attention. For each domain, a composite score was derived by the procedure of Townes et al[8]; that is,

each component score of the domain was standardized by subtraction of the mean and division by the SD of the preoperative scores for both groups combined. The mean of the standardized component scores was used as the score for the domain. On the basis of data from pilot series and the work of others,[9] it was decided a priori that patients would be classified as cognitively impaired if they realized a decrease of ≥0.5 SD compared with preoperative values in 1 or more of the 3 domains. The primary outcome was the incidence of cognitive impairment at the early postoperative assessment. This was compared by χ^2 test for all patients who completed the early postoperative testing. All other analyses of psychometric data were based on the intention-to-treat principle, by which all patients randomized to 1 of the 2 therapeutic strategies were included in the analysis according to treatment assignment. The method of last observation forward and other modeling procedures were used when necessary. Student's *t* test for independent samples was used to compare the 2 therapeutic strategies on the change from baseline to early or late postoperative visit. When needed, logistic regression analysis was used to make comparisons, with adjustment for covariates.

Sample size was based on detecting a 25% relative reduction in the early postoperative incidence of deficits from an expected rate of 60% in the control group to 45% in the hypothermic group. This difference could be detected with a sample of 150 per group (α=0.05, β=0.20). The study was terminated, for funding reasons, after 223 patients had been randomized. Results in the text are mean±SD.

Results

The preoperative (Table 1) and intraoperative (Table 2) characteristics of patients in the 2 groups were closely matched. The temperature protocol was followed closely (Figure 2). After rewarming, nasopharyngeal temperatures were 36.9±0.3°C and 34.1±0.4°C in the control and hypothermic groups, respectively. On arrival in the intensive care unit (ICU), temperature in the control group had decreased to 35.3±0.6°C compared with 33.6±0.5°C in the hypothermic group. It was 3 hours before the control group reached a mean temperature of 36.8°C and 5 hours before the hypothermic group reached 36.6°C. The time from surgery to the early postoperative visit was 9.7±7.5 versus 9.8±7.5 days (P=0.943) in the control and hypothermic groups, respectively.

The primary outcome, the incidence of cognitive impairment at the early postoperative visit, was 62% (62/100) in the control group and 48% (45/94) in the hypothermic group (P=0.048). The relative risk for the hypothermic group was 0.77, with a 95% CI of 0.59 to 1.00. Figure 3 illustrates the pattern of deficits in each group.

Mean scores at the preoperative visit and change scores for individual tests and the domains are given in Table 3. We observed a beneficial effect of hypothermia on 2 domains: attention and speed. The magnitude of deterioration in score was reduced by 56% for attention (P=0.038) and 41% for speed (P=0.042) in the hypothermic group. The hypothermic group showed significantly less deterioration on Digits Backward early after surgery. Scores for Digits Forward and Digits Backward were, however, significantly (P=0.018 and 0.021, respectively) higher in the control group before surgery. Logistic regression analysis showed that preoperative performance in Digits Backward was not significantly related to the likelihood of postoperative cognitive deficits (POCDs), and the adjusted effect of temperature was still significantly related to outcome even with baseline Digits Backward retained in the model.

At the 3-month visit, the performance of the 2 groups was still significantly different on the grooved pegboard test. Early after surgery, the control group required an average of 15.8 seconds longer than before surgery to complete the task, whereas the hypothermic group's time increased by 7.1 seconds (P=0.013). At 3 months, the difference persisted (P=0.003); the control group's time was still prolonged by 5.7 seconds, whereas the hypothermic group could now complete the task on average 2.6 seconds faster than before surgery. There were no significant differences between the groups in other psychometric tests at 3 months.

TABLE 1. Preoperative Characteristics of Patients

Characteristic	Control Group (n=112)	Hypothermic Group (n=111)
Age, y	68±6	68±5
Male sex	95 (85)	94 (85)
Education		
Grade 8 or less	33 (29)	40 (36)
Grade 9–12	39 (35)	32 (29)
College/university	40 (36)	39 (35)
Left ventricle class*		
Normal	38 (34)	35 (32)
1	26 (23)	18 (16)
2	25 (22)	27 (24)
3	15 (13)	18 (16)
4	6 (5)	7 (6)
Unknown	2 (2)	6 (5)
CCS		
1	8 (7)	9 (8)
2	20 (18)	20 (18)
3	64 (57)	66 (59)
4	18 (16)	14 (13)
Unknown	2 (2)	2 (2)
NYHA		
1	72 (64)	76 (68)
2	24 (21)	15 (14)
3	13 (12)	19 (17)
4	3 (3)	1 (1)
Diabetes mellitus treatment		
No disease	85 (76)	85 (77)
Diet	5 (4)	4 (4)
Oral	18 (16)	17 (15)
Insulin	4 (4)	5 (4)
Urgent cases	15 (13)	18 (16)
Previous CABG	11 (10)	17 (15)
Modified Mini-Mental State exam	95±4	95±5

Values are mean±SD or n (%). CCS indicates Canadian Cardiovascular Society angina classification; NYHA, New York Heart Association functional classification; and Urgent cases, patients admitted for control of unstable angina who were stabilized and proceeded to surgery on same admission.

*Left ventricle class: ventriculogram in right anterior oblique projection is divided into 4 segments. Left ventricle class is number of akinetic segments.

TABLE 2. Operative Characteristics

Characteristic	Control (n=112)	Hypothermic (n=111)	P
CPB time, min	83±27	87±26	0.264
Aortic cross-clamp time, min	46±18	47±14	0.563
Coronary artery bypass grafts	3±0.8	3±0.8	0.875
Glucose, mmol/L*	6.5±13	6.5±1.4	0.808
Hematocrit*	0.25±0.04	0.25±0.04	0.883
Nasopharyngeal temperature at end of CPB, °C	36.9±0.3	34.1±0.4	<0.001
Bladder temperature at end of CPB, °C	36.0±0.7 (n=111)	34.0±0.3 (n=109)	<0.001
Temperature on arrival in ICU, °C†	35.3±0.6	33.6±0.5	<0.001
Intra-aortic balloon pump, n (%)	1 (0.9)	6 (5.4)	0.053
Inotrope infusions, n (%)	11 (9.8)	17 (15.3)	0.216

Values are mean±SD or as indicated.
*Measured at start of rewarming; 1 mmol/L=18.02 mg/dL.
†Temperatures were equal at all sites by the time of arrival in ICU.

There was no effect of temperature on measures of mood or anxiety (Geriatric Depression Scale and State-Trait Anxiety Inventory). With the Canadian Neurological Scale, no focal deficits were discovered in either group at any examination. One patient in the control group suffered delirium immediately after surgery, and this persisted for several days.

Four patients died. One control patient developed mediastinitis and died 4 months after surgery. Three patients from the hypothermic group had uneventful hospital courses, were discharged, and died before the 3-month visit. The intra-aortic balloon pump was used more frequently in the hypothermic group (Table 2); 3 of the 6 hypothermic patients had previous CABG, whereas the control patient did not. Logistic regression analysis indicated that previous CABG was a significant predictor of intra-aortic balloon pump use, but temperature group was not. There was no difference in the incidence of Q-wave myocardial infarctions, total CK, CK-MB fraction, or number of patients with CK-MB >60 U/L. There were no differences in the duration of ventilator support, wound infections, length of stay in the ICU, or length of hospital stay (Table 4). Blood loss from chest tube drainage during the first 12 hours in the ICU and blood product use was similar between groups. During the first 12 postoperative hours, temperature measured in the pulmonary artery exceeded 38°C in 26% of control patients and 20% of hypothermic patients; for 39°C, the incidence was 3% of controls and 0% in the hypothermic group. These proportions were not statistically significantly different.

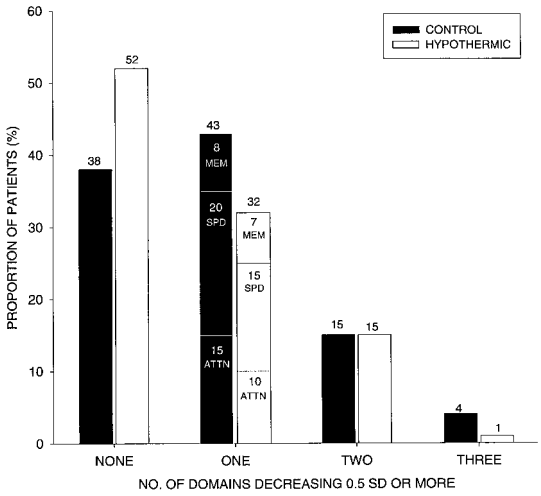

Figure 3. Pattern of deficits at early postoperative visit. Deficit was defined as deterioration in score of ≥0.5 SD compared with preoperative score in cognitive domain. Cognitive domains were memory (MEM), psychomotor speed and dexterity (SPD), and attention (ATTN). Among patients with deficit in only 1 domain, difference between groups was largely in domains of attention and speed. Data are proportions and include 100 control and 94 hypothermic patients who completed early postoperative testing.

Discussion

We found that mild hypothermia during and after CPB attenuated the cognitive decline found early after surgery in patients undergoing CABG. This was demonstrated both by a significant reduction in the number of patients with cognitive deficits in the hypothermic group and by a significant reduction in the magnitude of deterioration of mean change scores. A remarkable result was the difference between groups in the grooved pegboard test, where the performance of the hypothermic group was consistently and highly significantly better than the control group at both the early postoperative visit and the 3-month follow-up visit, which suggests a permanent benefit. These beneficial effects of hypothermia were not associated with any increase in postoperative morbidity or mortality or length of ICU or hospital stay.

POCDs after cardiac surgery have been documented extensively, with incidence ranging from between 30% and 80% early after surgery to 0% to 30% ≥3 months after surgery.[1] Some of the variability has been due to varying definitions of what constitutes a significant deterioration. The present research followed the guidelines of a consensus forum[10] on POCD in that we chose as a primary outcome a comparison of the incidence of deficits in each group. The

TABLE 3. Results of Cognitive Testing at Early Postoperative Visit*

Variable	Preoperative		Early Postoperative Change†		Effect of Treatment, Mean (95% CI)‡	Relative % Change§
	Control (n=112)	Hypothermic (n=111)	Control (n=112)	Hypothermic (n=111)		
Memory¶			0.20±0.8	0.14±0.8	−0.07 (−0.3 to 1.5)	−32
BFR	40.2±8.8	41.1±8.6	2.3±7.2	1.6±8.1	−0.7 (−2.7 to 1.3)	−31
BCLTR	18.7±12	20.4±12.7	2.8±12.3	2.2±12.0	−0.6 (−3.8 to 2.6)	−22
BLTR	24.7±12.5	26.1±13	3.8±11.6	2.6±11.7	−1.1 (−4.2 to 1.9)	−30
BLTS	27.5±13.0	29.0±13.0	4.2±12.4	2.4±11.4	−1.8 (−4.9 to 1.4)	−42
BDR	6.0±2.8	6.1±2.8	−0.2±2.1	−0.2±2.4	0.07 (−0.5 to 0.7)	30
Attention‖			−0.27±0.5	−0.12±0.5	0.15 (0.01 to 0.29)	56
DIGFOR¶	8.0±2.2	7.2±2.5	−0.4±1.6	−0.1±1.7	0.24 (−0.2 to 0.7)	64
DIGBACK¶	6.7±2.5	5.9±2.4	−0.9±1.8	−0.4±1.8	0.49 (0.01 to 0.96)	54
Speed‖			−0.46±0.8	−0.27±0.6	0.19 (0.01 to 0.37)	41
SDMT	43.1±10.1	42.1±11.0	−4.6±7.3	−3.1±5.5	1.4 (−0.3 to 3.1)	31
Trails A	39.4±12.0	39.8±12.3	3.3±14.9	2.0±13.7	−1.3 (−5.1 to 2.5)	−40
Trails B	106±50.3	109±47.7	15.3±43.3	12.3±40.8	−2.9 (−14.1 to 8.2)	−19
PEGTIME	87.5±19.6	89.0±19.5	15.8±31.9	7.1±19.1	−8.8 (−15.7 to −1.8)	−55

BFR indicates Buschke total learning free recall; BCLTR, Buschke consistent long-term retrieval; BLTR, Buschke long-term retrieval; BLTS, Buschke long-term storage; BDR, Buschke delayed recall; DIGFOR, Digit Span Forward; DIGBACK, Digit Span Backward; SDMT, Symbol Digit Modalities Test; and PEGTIME, grooved pegboard.

*Intention-to-treat analysis; see Methods. Values are mean±SD.

†Early postoperative score − preoperative score. Increase in score indicates improved performance on all tests except the 3 timed tests (Trails A, Trails B, PEGTIME), where increases indicate worsened performance.

‡Change in hypothermic − change in control.

§Effect of treatment as a percent of change in control group. For the Buschke variables and DIGFOR, DIGBACK, and SDMT, positive relative % change indicates better performance by the hypothermic group. For Trails A, Trails B, and PEGTIME, negative % relative change indicates better performance by the hypothermic group.

‖The domain scores are the average of the z scores for the component subtests. The sign of the z score is adjusted so that a positive change indicates improved performance by the hypothermic group. By definition, preoperative z scores have a value close to 0.

¶Scores for DIGFOR and DIGBACK were greater in the control group preoperatively (P=0.018 and 0.021, respectively).

classification of patients into those with and without deficits was recommended because a benefit to patients with cerebral injury can be obscured, in the analysis of mean change scores, by the inclusion of patients who have not suffered injury and whose scores improve after surgery. Others[11] have suggested that group mean analysis is the most reliable method if a control group is available. In the present trial, group mean change scores in 2 of the 3 cognitive domains evaluated did support the results of the incidence analysis.

Evidence that POCDs after cardiac surgery are due to ischemic cerebral injury includes autopsy[3] and animal studies[12] that demonstrated histological evidence of embolization, as well as noninvasive studies of patients during CPB that demonstrated the frequent occurrence of embolic material in the cerebral circulation.[13] Some have demonstrated a correlation between the frequency of emboli detected with transcranial Doppler and POCD.[14] POCDs are also observed after major noncardiac surgery,[2] but with a lower frequency. If hypothermia reduces the incidence of POCD of ischemic origin only, and if a proportion of the POCDs observed in the present study were nonischemic, then the present findings would underestimate the beneficial effect of hypothermia on ischemic POCD.

Our assessment battery included speeded measures of attention, concentration, and memory because neuropsychological models of brain-behavior relationships would predict that these would be the most sensitive tools with which to detect ischemic insults, especially later in the recovery stage.[9] We included the core tests recommended by the consensus conference on POCDs.[15] We found our measure of memory and verbal learning to be insensitive to the temperature treatment, and it failed to show the expected deterioration after surgery. Practice effects may have eclipsed the expected changes despite the use of alternate forms.

There was a beneficial effect of hypothermia on attention. However, at the preoperative visit, the control group performed better than the hypothermic group. We are unable to explain this isolated baseline difference. It may have increased the treatment effect because of regression to the mean, ie, the tendency of high-scoring individuals to score lower on a second test in the absence of true change. Because the difference was small and there is typically a good correlation between repeated tests, it is likely that the effect of regression to the mean was small.[16] Logistic regression analysis indicated that the preoperative score did not have a significant effect on the likelihood of cognitive deficits.

Tests of psychomotor speed and dexterity, such as the grooved pegboard, are known to be sensitive indicators of the presence of generalized brain dysfunction. Patients in the control group suffered significantly more motor slowing and at 3 months remained slower than before surgery. The hypothermic patients, in contrast, performed the pegboard task faster at 3 months after surgery than before surgery. The consistency of the difference between groups in this test was

TABLE 4. Safety Outcomes

Outcome	Control (n=112)	Hypothermic (n=111)	*P*
Hours to extubation	16±17	16±12	0.749
Days in ICU	1.6±2	1.9±5	0.445
Median	1.0	1.0	
Days in hospital	8.3±13	7.5±6	0.539
Median	6	7	
Incidence of infection, n (%)	6 (5)	4 (4)	0.527
12-Hour blood loss in ICU, mL	812±493	858±592	0.526
Blood utilization in ICU			
Autotransfusion, mL*	445±401	348±341	0.053
Packed red blood cells, U	0.45±0.98	0.59±1.3	0.374
Fresh frozen plasma, U	0.27±0.9	0.37±1.1	0.463
Platelets, U	0.69±2.2	0.72±2.3	0.911
Predonated autologous blood, U	0.33±0.83	0.18±0.51	0.105
Q-wave myocardial infarction, n (%)	3 (2.7)	1 (0.9)	0.622
Mortality, n (%)	1 (0.9)	3 (3)	0.309

Values are mean±SD or n (%).

*Autotransfusion is the amount of mediastinal shed blood returned to the patient while in the ICU.

remarkable, and the probability of this finding at the 3-month follow-up being due to chance ($P=0.003$) is very low even if corrected for multiple testing. The persistence of the group difference at 3 months suggests a permanent neuroprotective benefit of mild hypothermia. Newman et al[17] reported that patients undergoing coronary artery surgery who showed impaired cognitive function at discharge from hospital appeared to recover after several months, but when tested at 5 years, they again demonstrated significant impairment. Those who are not impaired at discharge do not suffer a similar late decline. These findings support the possibility that an intervention that reduces the incidence of early postoperative cognitive decline may improve long-term function even if the effect is not apparent 3 months after surgery.

The incidence of focal neurological deficits in patients undergoing CABG is 1% to 3% in most series.[18] The low incidence in the present study may be due to the exclusion of emergencies and patients with a history of neurological events or renal failure. The Canadian Neurological Scale has been shown to be a valid and reliable method of documenting the effects of stroke.[6]

There was no evidence of adverse effects of hypothermia. Specifically, there were no differences in bleeding, infection, cardiac outcomes, or length of stay in ICU or hospital. Although the temperature of the control group on arriving in the ICU (35.3°C) was typical for cardiac surgical patients undergoing CPB, it was not normothermic. It is possible that safety outcomes would be different if the hypothermic group were compared with a truly normothermic group (>36°C). Nevertheless, both groups in the present study had low complication rates. The safety of extended mild hypothermia for those at high risk (eg, renal failure, emergencies, or previous stroke) is not supported by the present data, because such patients were excluded.

Despite the marked neuroprotective effect of hypothermia in laboratory studies, conclusive proof of efficacy in patients has been lacking. Martin et al[19] compared outcomes after normothermic versus hypothermic CPB for CABG and found a rate of neurological deficits of 3.1% in the normothermic group compared with 1.0% in the hypothermic group. This may have been due to an increased incidence of injury in the normothermic group due to perfusion at temperatures exceeding 37°C or to the use of retrograde cardioplegia rather than to a protective effect of hypothermia, because others[18,20] have not confirmed this experience. McLean et al[21] were the first to address the question of the effect of CPB temperature on POCD and found no benefit of CPB at 28°C compared with 34°C. Mora et al[22] and Regragui et al[23] provide data suggestive but not conclusive of a beneficial effect of hypothermia after CPB. Three recent studies[20,24,25] found no benefit of different degrees of hypothermia during CPB on neuropsychological outcome of CABG. A common characteristic of these studies is rewarming of all patients before separation from CPB, often to temperatures exceeding 37°C. Thus, the duration of exposure to a beneficial effect of hypothermia was brief, and these patients were still exposed to the possibly deleterious effects of cerebral hyperthermia during rewarming.[26] In contrast to standard practice, we avoided raising nasopharyngeal temperature above 37°C during rewarming in both our groups. During rewarming in the normothermic group, the blood in the pump-oxygenator likely was warmed to 38°C for 5 to 10 minutes (we monitored but did not record these temperatures). Our study design cannot exclude a deleterious effect of this transient hyperthermia on the outcome. The present study is unique in that the period of hypothermia was extended into the postoperative period. We believe that the neuroprotection observed is most likely due to the marked modulation of ischemic injury by mild hypothermia shown in laboratory studies.[5] The present data, however, do not exclude the possibility that the small decrease in cerebral blood flow expected with a 2°C to 3°C lowering of temperature may have reduced embolic load during CPB.

We have demonstrated a reduction in the incidence and severity of cognitive deficits with the use of an extended period of mild hypothermia in patients undergoing coronary artery surgery. Our results also suggest that the neuroprotective benefit is long lasting and is not associated with an increase in morbidity or length of hospital stay. Our findings should encourage physicians and perfusionists to pay careful attention to brain temperature during CPB. Further research is required to confirm the mechanism of benefit demonstrated and to determine whether this therapeutic strategy can be used for patients with other forms of ischemic cerebral injury, such as stroke.

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